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24 JAN 1997

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference PHM 97/004

2. Patent application number *(The Patent Office will fill in this part)* **9701417.9**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
ZENECA Limited
15 Stanhope Gate
LONDON W1Y 6LN, United Kingdom
Patents ADP number *(if you know it)*
6254007002
If the applicant is a corporate body, give the country/state of its incorporation

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4. Title of the invention
CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*
GILES, Allen Frank
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
Intellectual Property Department
ZENECA Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire, SK10 4TG, United Kingdom
Patents ADP number *(if you know it)* 6988463001

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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Joanne Chilton Date 23 JAN 1997

12. Name and daytime telephone number of person to contact in the United Kingdom JOANNE CHILTON - 01625 516485.

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CHEMICAL COMPOUNDS

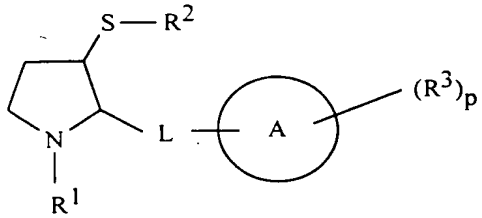
This invention relates to compounds that inhibit farnesylation of mutant ras gene products through inhibition of the enzyme farnesyl-protein transferase (FPTase). The invention also relates to methods of manufacturing the compounds, pharmaceutical compositions and methods of treating diseases, especially cancer, which are mediated through farnesylation of ras.

Cancer is believed to involve alteration in expression or function of genes controlling cell growth and differentiation. Whilst not wishing to be bound by theoretical considerations the following text sets out the scientific background to ras in cancer. Ras genes are frequently mutated in tumours. Ras genes encode guanosine triphosphate (GTP) binding proteins which are believed to be involved in signal transduction, proliferation and malignant transformation. H-, K- and N-ras genes have been identified as mutant forms of ras (Barbacid M, Ann. Rev. Biochem. 1987, 56: 779-827). Post translational modification of ras protein is required for biological activity. Farnesylation of ras catalysed by FPTase is believed to be an essential step in ras processing. It occurs by transfer of the farnesyl group of farnesyl pyrophosphate (FPP) to a cysteine at the C-terminal tetrapeptide of ras in a structural motif called the CAAX box. After further post-translational modifications, including proteolytic cleavage at the cysteine residue of the CAAX box and methylation of the cysteine carboxyl, ras is able to attach to the cell membrane for relay of growth signals to the cell interior. In normal cells activated ras is believed to act in conjunction with growth factors to stimulate cell growth. In tumour cells it is believed that mutations in ras cause it to stimulate cell division even in the absence of growth factors (Travis J, Science 1993, 260: 1877-1878), possibly through being permanently in GTP activated form rather than cycled back to GDP inactivated form. Inhibition of farnesylation of mutant ras gene products will stop or reduce activation.

One class of known inhibitors of farnesyl transferase is based on farnesyl pyrophosphate analogues: see for example European patent application EP 534546 from Merck. Inhibitors of farnesyl transferase based on mimicry of the CAAX box have been reported. Reiss (1990) in Cell 62, 81-8 disclosed tetrapeptides such as CVIM (Cys-Val-Ile-Met). James (1993) in Science 260, 1937-1942 disclosed benzodiazepine based peptidomimetic compounds. Lerner (1995) in J. Biol. Chem. 270, 26802 and Eisai in

International Patent Application WO 95/25086 disclosed further peptidomimetic compounds based on Cys as the first residue. Bristol-Myers Squibb in European Patent Application EP 696593 disclosed for the first time farnesyl transferase inhibitors having a 4-sulfanylpyrrolidine residue in the first position. It is believed that there has been no disclosure of such compounds having a 3-sulfanyl pyrrolidine moiety in the first position.

According to one aspect of the present invention there is provided an inhibitor of ras farnesylation of Formula I



Formula I

wherein:

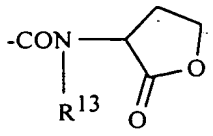
R^1 is selected from H; -C_{1-4}alkyl; -C_{1-3}alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4}alkyl, halogen, OH, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, thiol, C_{1-4}alkylsulfanyl, C_{1-4}alkylsulfinyl.C_{1-4}alkylsulfonyl and sulfonamido; -CO-C_{1-4}alkyl; -CO-O-C_{1-4}alkyl; -CO-O-C_{2-4}alkenyl; -CO-O-$(CH_2)_n$Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above and n=0-4; -C_{1-4}alkylene-$CONR^4R^5$ where R^4 & R^5 are independently selected from H and C_{1-4}alkyl; and -C_{1-4}alkylene-$COOR^6$ where R^6 is selected from H, C_{1-4}alkyl;

R^2 is selected from H; -C_{1-4}alkyl; -C_{1-3}alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above; -COC_{1-4}alkyl; and -$COOC_{1-4}$alkyl;

R^3 is selected from H; OH; CN; CF_3; NO_2; -C_{1-4} alkyl; -C_{1-4}alkylene-R^7 where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O,N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in R^1 = -C_{1-3}alkylene-Ph above; R^7; C_{2-4}alkenyl; halogen; -$(CH_2)_nCOOR^8$ where n= 0-3 and R^8 represents H, C_{1-4}alkyl, or C_{2-4}alkenyl; -$CONR^9R^{10}$ where R^9 and R^{10} independently represent H,

C_{1-4}alkyl, C_{2-4}alkenyl, -O-C_{1-4}alkyl, -O-C_{2-4}alkenyl, -C_{1-3}alkylenePh optionally substituted as defined for this group for R^1 above;-CON(R^{11})OR^{12} where R^{11} and R^{12} independently represent H, C_{1-4}alkyl and C_{2-4}alkenyl;

a group of Formula II, -CONR^{13}-CHR^{14}-COOR^{17} , where R^{13} is H or C_{1-4}alkyl, R^{17} is H or C_{1-6}alkyl, R^{14} is selected from the side chain of a lipophilic amino acid, carbamoylC_{1-4}alkyl, N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl and N-(diC_{1-4}alkyl)carbamoylC_{1-4}alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



;

C_{1-4}alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R^{15} where X is selected from O, CO, CH_2, S, SO, SO_2 and R^{15} is selected from C_{1-6}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O,N and S and any aryl ring in R^{15} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph;

p is 0-3 in which R^3 values can be the same or different;

L is a linking moiety selected from the following groups written from left to right in Formula I:

-CO-NR^{16}- where R^{16} is selected from H, C_{1-4}alkyl, C_{1-4}alkylene-Z, -CO-C_{1-4}alkylene-Z, -CO-C_{1-6}alkyl, -COZ, Z and Z is selected from -O-C_{1-4}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms selected from O, N and S and any aryl ring in R^{16} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph; -CH_2-NR^{18}- where R^{18} represents any value defined for R^{16}; -CH_2S-; -CH_2O-; -CH_2-CHR^{19}- where R^{19} represents any value defined for R^{16}; -CH=CR^{20}- where R^{20} represents any value defined for R^{16}; -CH_2NR^{21}-T- where R^{21} represents any value defined for R^{16}, T represents -$(CH_2)_n$- where n is 1-4 and T is optionally monosubstituted with R^{22} where R^{22} represents any value for R^{16} other than H; -CH_2NR^{23}-SO_2- where R^{23} represents any value defined for R^{16}; -CH_2-NR^{24}-CO-T- where R^{24} represents any value defined for R^{16}, T represents -$(CH_2)_n$- where n is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H;

-CO-NR^{25}-T- where R^{25} represents any value defined for R^{16}, T represents -$(CH_2)_n$- where n is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for other than H; -CH_2S-T- where T represents -$(CH_2)_n$- where n is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; -CH_2O-T- where T represents -$(CH_2)_n$- where n is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing upto 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R^2=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.

In another aspect of the invention the group of Formula II is expanded to allow substitution of H by C_{1-4}alkyl at the α carbon (to which R^{14} is attached) such that Formula II becomes -CONR^{13}-CR^{13a}R^{14}-COOR^{17} where R^{13a} represents H or C_{1-4}alkyl and other variable groups take any of the values (ranging from general to specific within the scope of Formula I) described herein.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms

The term " halogen " refers to fluorine, chlorine, bromine and iodine. The term " carbamoyl " refers to -$C(O)NH_2$. The term " BOC " refers to tert-butyl-O-C(O)-. The term " allyl " refers to CH_2=CH-CH_2-. Bicyclic aryl and bicyclic heteroaryl rings refer to ring systems in which both rings of the bicyclic system are aromatic.

Examples of **C_{1-6}alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl and pentyl; examples of **C_{1-4}alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl and *tert*-butyl; examples of **C_{1-3}alkyl** include methyl, ethyl, propyl and isopropyl; examples of **-C_{1-3}alkylenePh** include benzyl, phenylethyl, phenylpropyl; examples of **C_{1-4}alkoxy** (also called **-O-C_{1-4}alkyl** herein) include methoxy, ethoxy and propoxy; examples of **C_{1-4}alkanoyl** include formyl, acetyl and propionyl; examples of **C_{1-4}alkanoyloxy**

include acetyloxy and propionyloxy; examples of **C_{1-4}alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of **di-(C_{1-4}alkyl)amino** include di-methylamino, di-ethylamino and N-ethyl-N-methylamino; examples of **C_{1-4}alkanoylamino** include acetamido and propionylamino; examples of **C_{1-4}alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **C_{1-4}alkylsulfanyl** include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, *sec*-butylsulfanyl and *tert*-butylsulfanyl; examples of **C_{1-4}alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl and *tert*-butylsulfinyl; examples of **C_{1-4}alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl; examples of **-CO-C_{1-4}alkyl** include formyl, acetyl, propionyl, butyryl, and valeryl; examples of **-CO-O-C_{1-4}alkyl** include ethyloxycarbonyl; propyloxycarbonyl and *tert*-butyloxycarbonyl (BOC); examples of **-CO-O-C_{2-4}alkenyl** include allyloxycarbonyl and vinyloxycarbonyl; examples of **-CO-O-$(CH_2)_n$Ph** where n=0-4 include phenyloxycarbonyl, benzyloxycarbonyl, phenylethyloxycarbonyl and phenylpropyloxycarbonyl; examples of **-C_{1-4}alkylene-CONR^{4}R^5** include carbamoylmethyl, carbamoylethyl, N-methylcarbamoylethyl, N-methyl-N-ethylcarbamoylethyl; examples of **-C_{1-4}alkylene-COOR^6** include carboxymethyl, carboxyethyl, carboxypropyl, propionic acid methyl ester, acetic acid ethyl ester; examples of **C_{2-4}alkenyl** include allyl and vinyl; examples of **-O-C_{2-4}alkenyl** include allyloxy and vinyloxy; examples of **lipophilic amino acids** include valine, leucine, isoleucine, methionine, phenylalanine, serine, threonine and tyrosine; examples of **carbamoylC_{1-4}alkyl** include carbamoylmethyl, carbamoylethyl and carbamoylpropyl; examples of **N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl** include N-methyl-carbamoylmethyl and N-ethyl-carbamoylethyl; examples of **N-(diC_{1-4}alkyl)carbamoyl-C_{1-4}alkyl** include N,N-dimethylcarbamoylethyl and N-methyl-N-ethylcarbamoylethyl; examples of **C_{1-4}alkyl monosubstituted on carbon with =N-OH** include butyraldehyde oxime and propionaldehyde oxime; examples of **hydroxyC_{1-6}alkyl** include hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, 2-(hydroxymethyl)propyl and hydroxypentyl; examples of **C_{1-6}alkoxyC_{1-6}alkyl** include methoxyethyl, ethoxyethyl and methoxybutyl; examples of **C_{1-6}alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl and

pentylcarbonyl; examples of **hydroxyC_{1-6}alkylcarbonyl** include hydroxyacetyl, hydroxypropionyl, hydroxybutyryl, 3-hydroxybutyryl and hydroxypentanoyl; examples **C_{1-6}alkoxyC_{1-6}alkylcarbonyl** include methoxyacetyl, methoxypropionyl, ethoxybutyryl and butoxyacetyl; examples of **phenylC_{1-6}alkyl** include benzyl, phenylethyl and phenylpropyl; examples of **-CO-C_{1-4}alkyl-Ph** include phenylacetyl and phenylpropionyl; examples of **-CO-C_{1-4}alkyl-heteroaryl** include 2-(3-pyridyl)-acetyl and 2-(3-thienyl)-acetyl; examples of **N-(C_{1-6}alkyl)carbamoyl** include N-methyl-carbamoyl and N-ethyl-carbamoyl; examples of **N-(diC_{1-6}alkyl)carbamoyl** include N,N-dimethylcarbamoyl and N-methyl-N-ethylcarbamoyl.

Examples of **5-10 membered monocyclic or bicyclic heteroaryl rings containing upto 5 heteroatoms selected from O,N and S** include the following.
Examples of 5- or 6-membered heteroaryl ring systems include imidazole, triazole, pyrazine, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole and thiophene. A 9 or 10 membered bicyclic heteroaryl ring system is an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine.

Preferably monocyclic heteroaryl rings contain upto 3 heteroatoms and bicyclic heteroaryl rings contain upto 5 heteroatoms. Preferred heteroatoms are N and S, especially N. In general, attachment of heterocyclic rings to other groups is via carbon atoms. Suitable values of heterocycles containing only N as the heteroatom are pyrrole, pyridine, indole, quinoline, isoquinoline, imidazole, pyrazine, pyrimidine, purine and pteridine.

Examples of lipophilic amino acids which contribute their side chain (denoted R^{14} within the definition of values for R^3) include methionine, phenylglycine, phenylalanine, serine, leucine, isoleucine or valine. L configuration in the corresponding free amino acid is preferred. Examples of amino acid side chains are set out below. A preferred value for R^{14} is $-CH_2-CH_2-S-CH_3$. Further preferred values for R^{14} are $-CH_2-OMe$ and $-CH_2-CH_2-OMe$.

When R^{17} is H to give a COOH group in Formula II, and R^{14} is $-CH_2-CH_2-OH$ then a lactone can be formed where R^{17} and R^{14} together form part of a dihydrofuran-2-one heterocyclic ring. The same lactone can be formed for compounds of Formula III where X^4 is OH and X^3 is H.

Amino Acid	**Side Chain**
methionine	$-CH_2-CH_2-S-CH_3$
phenylglycine	Ph
phenylalanine	$-CH_2-Ph$
serine	$-CH_2OH$ or a C_{1-4}alkyl (preferably methyl) ether thereof.
leucine	$-CH_2-CHMe_2$
homoserine	$-CH_2-CH_2-OH$ or a C_{1-4}alkyl (preferably methyl) ether thereof.

Preferably $\mathbf{R^1}$ is selected from H; $-CO-O-(CH_2)_n$Ph optionally substituted on Ph as defined for R^1 = $-C_{1-3}$alkylene-Ph and n=0-4; $-CO-O-C_{2-4}$alkenyl; $-CO-C_{1-4}$alkyl; $-C_{1-4}$alkylene-$CONR^4R^5$ where R^4 & R^5 are independently selected from H, C_{1-4}alkyl.

Preferably $\mathbf{R^2}$ is selected from H and $-CO-C_{1-4}$alkyl.

Preferably **L** is selected from $-CH_2-NR^{18}-$; $-CH_2NR^{21}-T$.

Preferably **A** is selected from phenyl, naphthyl, pyridyl and thienyl.

Preferably combinations of $\mathbf{R^3}$ and **p** are selected from:

i) R^3 is selected from a group of Formula II; $-C_{1-4}alkylR^7$; $-O-R^7$ and; R^7; and p=1-3 with the proviso that one value of R^3 is a group of Formula II;

ii) p=0 with the proviso that A is naphthyl and L is $-CH_2NR^{21}-T$;

iii) p=1 with the proviso that R^3 = a group of Formula II and A is naphthyl.

Suitable pairs of values for R^3 when p=2 are: -COOMe, -CO.N(Me).OMe; NO_2, -CO.N(Me).OMe; -COOMe, allyloxycarbonyl; -CO.N(Me).OMe, allyloxycarbonyl; allyloxycarbonyl, $-CO.N(Me).O.CH_2CH=CH_2$; OH, COOH; -COOMe, COOMe; Ph, -CO.N-Methionine methyl ester; Ph, -CO.N-Methionine; benzyl, -CO.N-Methionine methyl ester; benzyl, -CO.N-Methionine; benzyl, -CO.N-Methionine isopropyl ester; Ph, -CO.Nα-Glutamine methyl ester; Ph, -CO.Nα-Glutamine.

Suitable values for L= $CHNR^{21}T$ include $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$; $CH_2.N(CH_2\ CH_2\ CH_2OMe).CH_2.CH_2$; $CH_2.N(CH_2.pPh.OMe).CH_2.CH_2$;

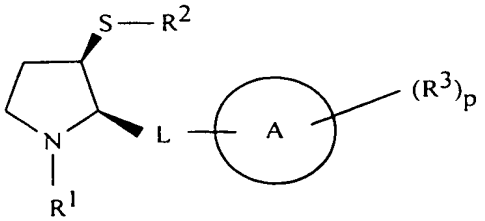
$CH_2.N(CO.CH_2.CHMe_2).CH_2$; $CH_2N(CO.CH_2.CH_2.CH_2.Me).CH_2$; $CH_2N(CO.CH_2.CHMe.CH_2Me).CH_2$; $CH_2N(CO.CH_2.CH_2.OMe)CH_2$; $CH_2N(CO.CH_2.pyridin\text{-}3\text{-}yl).CH_2$; $CH_2N(4\text{-}methoxybenzyl)CH_2$; $CH_2N(CO.CH_2.CHMe_2)CH_2.CH_2.CH(Ph)$; $CH_2N(CO.CH_3)CH_2.CH_2.CH(Ph)$; $CH_2N(CO.CH_2.CHMe_2)CH_2$; $CH_2N(CO.CH_3)CH_2$; $CH_2N(CO.CH_2.CHMe_2)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.CMe_3)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.pyridin\text{-}3\text{-}yl)CH_2.CH(Ph)$; $CH_2N(CO.1\text{-}hydroxy\text{-}6\text{-}methoxy\text{-}pyridin\text{-}3\text{-}yl)CH_2.CH(Ph)$; $CH_2N(CO.CH_2CHMe_2)CH_2.CH_2$; $CH_2N(CO.CH_2CMe_3)CH_2.CH_2$; $CH_2N(CO.CH_2pyridin\text{-}3\text{-}yl)CH_2.CH_2$; $CH_2N(CO.4\text{-}methoxybenzyl)CH_2.CH_2$;

Suitable values for L = $-CH_2NR^{18}-$ include CH_2NH; CH_2NMe; $CH_2N(CO.CH_2.CHMe_2)$ and $CH_2N(CO.CH_2.CH_2.OMe)$.

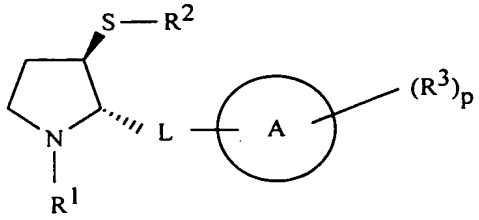
When L is $-CH_2NR^{21}$-T- a suitable value for n is 1. When L is $-CH_2\cdot NR^{24}$-CO-T- a suitable value for n is 1. When L is $-CH_2\cdot NR^{25}$-T- a suitable value for n is 1. When L is $-CH_2\cdot$S-T- a suitable value for n is 1. When L is $-CH_2\cdot$O-T- a suitable value for n is 1. L is especially -CONH-, $-CH_2$-NH-, $-CH_2NHSO_2$-, $-CH_2NHCO$-.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting FTPase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against FTPase may be evaluated using the standard laboratory techniques referred to hereinafter.

Preferably any chiral carbon atoms at the 2 and 3 positions of the pyrrolidine ring in Formula I has the configuration indicated below. Generally the chiral carbon atoms are in R configuration under the Cahn-Prelog-Ingold sequence rules.

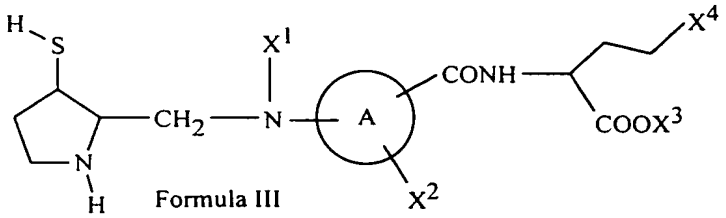


Another suitable stereochemistry is indicated below .



Preferred compounds of the invention are any of the following classes i), ii) or iii) of compound:

class i)



Formula III

wherein:

X^1 is selected from H; C_{1-6}alkyl; hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl; C_{1-6}alkylcarbonyl; hydroxyC_{1-6}alkylcarbonyl; C_{1-6}alkoxyC_{1-6}alkylcarbonyl;

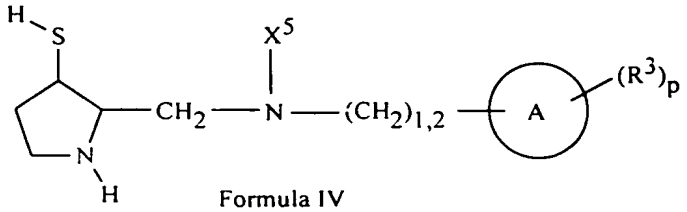
A is selected from phenyl, naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

X^2 is selected from H; phenyl; phenylC_{1-6}alkyl; a 5-6 membered heteroaryl ring containing upto 3 heteroatoms selected from O, N and S optionally linked to A by C_{1-6}alkyl; and X^2 is optionally substituted on any ring as defined for phenyl in R^1 = -C_{1-3}alkylene-Ph in claim 1;

X^3 is selected from H; C_{1-6}alkyl;

X^4 is selected from C_{1-6}alkylsulfanyl; C_{1-6}alkylsulfinyl; C_{1-6}alkylsulfonyl; carbamoyl; N-(C_{1-6}alkyl)carbamoyl; N-(diC_{1-6}alkyl)carbamoyl; and hydroxy or a C_{1-4}alkyl ether thereof;

class ii)



Formula IV

wherein:

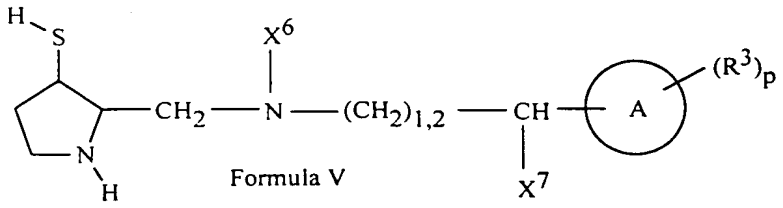
X^5 is selected from -CO-C_{1-4}alkyl-Ph; -CO-C_{1-6}alkyl; -CO-C_{1-4}alkyl-heteroaryl where heteroaryl is a 5-10 membered heteroaryl ring containing upto 5 heteroatoms selected : O, N and S and Ph or heteroaryl are optionally substituted as defined for Ph in R^1 = -C_{1-3}alkylene-Ph;

C_{1-4}alkyloxyC_{1-4}alkyl;

A is naphthyl or a 10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

R^3 and **p** are as defined above;

class iii)



Formula V

wherein:

X^6 has any value defined for X^5 in ii) above;

X^7 is Ph optionally substituted as defined for Ph in R^1 = -C_{1-3}alkylene-Ph;

A is Ph or naphthyl or a 5-10 membered heterocyclic ring having upto 5 heteroatoms selected from O, N and S;

R^3 and **p** are as defined above;

or a N-oxide, pharmaceutically acceptable salt, prodrug or solvate thereof .

Preferred values for compounds of class i) include,

X^1 is selected from H and C_{1-6}alkoxyC_{1-6}alkyl;

X^2 is selected from H; phenyl or phenylC_{1-6}alkyl;

X^4 is C_{1-6}alkylsulfanyl;

A is selected from phenyl or naphthyl;

Other preferred values for X^4 are -OMe and the lactone which can be formed when X^4 is OH and X^3 is H.

Preferred values for compounds of class ii) include **p** is 0.

Preferred values for compounds of class iii) include,

X^7 is Ph;

A is Ph;

p is 0.

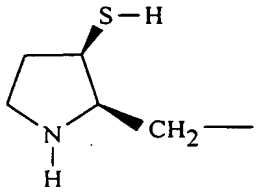
In another embodiment of the invention preferred values are set out below.

In compounds of Formula III: X^1 is H or methoxyC_{1-4}alkyl (especially H); X^2 is H, phenyl or benzyl (especially benzyl); X^3 is H or C_{1-4}alkyl (especially H); X^4 is C_{1-4}alkylsulfanyl (especially methylsulfanyl); and A is phenyl. When A is a 6-membered aryl or heteroaryl ring then groups $-NX^1-$ and the substituent comprising X^4 are preferably in meta juxtaopsition relative to each other; and X^2, if present, is preferably positioned para relative to $-NX^1-$. The chiral carbon to which $-COOX^3$ is attached is preferably in S configuration. The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration.

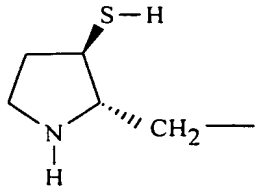
In compounds of Formula IV: X^5 is $-CO-C_{1-4}$alkyl (especially $-CO-CH_2-CHMe_2$) or $-CH_2-Ph-O-C_{1-4}$alkyl (especially $-CH_2-Ph-OMe$); heteroaryl is preferably pyridyl and a preferred aryl or heteroaryl substituent is $-O-C_{1-4}$alkyl (especially methoxy); and A is naphthyl. The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration. The attachment point for A relative to $-(CH_2)_{1,2}-$ is preferably at the 1 position of napththalene and the equivalent position for heterocyclic values for A (regardless of ring numbering conventions for heterocycles). A preferred value for $-(CH_2)_{1,2}-$ is $-(CH_2)_2-$.

In compounds of Formula V: X^6 is $-CO-C_{1-5}$alkyl (more preferably $-CO-CH_2-CHMe_2$ or $-CO-CH_2-t$-butyl, especially $-CO-CH_2-CHMe_2$) or $-CH_2-Ph-O-C_{1-4}$alkyl (especially $-CH_2-Ph-OMe$); heteroaryl is preferably pyridyl and a preferred aryl substitution is $-O-C_{1-4}$alkyl (especially methoxy); and A is phenyl or naphthyl (especially phenyl). The chiral carbons at the 2 and 3 positions of the pyrrolidine ring are preferably in R configuration. A preferred value for $-(CH_2)_{1,2}-$ is $-(CH_2)_1-$.

Preferably any chiral carbon atoms at the 2 and 3 positions of the pyrrolidine ring in Formulas III, IV or V has the configuration indicated below. Generally the chiral carbon atoms are in R configuration under the Cahn-Prelog-Ingold sequence rules.



Another suitable configuration is indicated below.



According to another aspect of the present invention there is provided any one of the following individual compounds or a pharmaceutically acceptable salt thereof:

(2S)-2-{2-Benzyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-{2-Benzyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid ;

(2S)-2-({2-phenyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({2-phenyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(2S)-2-({3-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;

(2S)-2-({-3-phenyl-5[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({-3-phenyl-5[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(2R,3R)-2-[{N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-3-thiol ;

N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-pentanamide;

N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide ;

N-((2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;

(2R,3R)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}- pyrrolidine-3-thiol;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide ;

(2R,3R)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}-pyrrolidine-3-thiol ;

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butyramide ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide ;

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butyramide ;

(2S)-2-{3-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide ;

(2S)-4-carbamoyl-2-({2-phenyl-5-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid;

(2S)-4-carbamoyl-2-({2-phenyl-5-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester;

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-acetamide;

6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

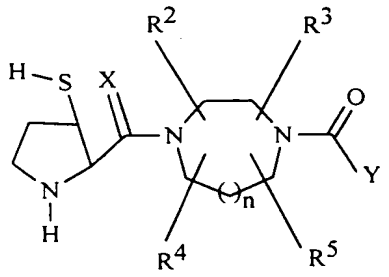
N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide;

6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

(2S)-2-{2-benzyl-4-[([2R,3R]3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid; and

(2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine.

In another aspect of the present invention there is provided a compound which inhibits farnesyl-protein transferase of the formula A:



A

wherein:

X is 0 or H_2;

n is 0 or 1;

t is 1 to 4;

R^2, R^3, R^4, and R^5 are independently selected from: H; C_{1-8}alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-NR^6R^7 or -CO-OR^6, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a. C_{1-4}alkyl,
   b. $(CH_2)_tOR^6$,
   c. $(CH_2)_tNR^6R^7$,
   d. halogen,
2) C_{3-6}cycloalkyl,
3) OR^6,
4) SR^6, $S(O)R^6$, SO_2R^6,
5) -NR^6R^7,
6) -NR^6-CO-R^7,
7) -NR^6-CO-NR^7R^8,

8) -O-CO-NR^6R^7,

9) -O-CO-OR^6,

10) -O-NR^6R^7,

11) -$SO_2NR^6R^7$,

12) -NR^6-SO_2-R^7,

13) -CO-R^6, or

14) -CO-OR^6;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4}alkyl, unsubstituted or substituted with:

a. C_{1-4}alkoxy,

b. NR^6R^7,

c. C_{3-6}cycloalkyl,

d. aryl or heterocycle,

e. HO,

2) aryl or heterocycle,

3) halogen,

4) OR^6,

5) NR^6R^7,

6) CN

7) NO_2, or

8) CF_3;

R^6, R^7 and R^8 are independently selected from: H; C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4}alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) -CO-R^9,

f) -SO_2R^9, or

g) NRR^1, wherein

R^6 and R^7 may be joined in a ring, and

R^7 and R^8 may be joined in a ring;

R^9 is C_{1-4}alkyl or aralkyl;

or a optical isomer, disulfide or pharmaceutically acceptable salt thereof.

This aspect of the invention relating to Formula A involves compounds related to those disclosed PCT patent application WO 95/00497 (Graham et al.); see the complete specification and claim 1 in particular. Formula A above is based on Formula A in WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidine moiety of the present invention replacing the cysteine-like moiety on the left hand side of Formula A in WO 95/00497 (Graham et al.). Optionally the nitrogen and/or thiol atoms in the pyrrolidine moiety of Formula A may be substituted by taking the values for R^1 and R^2 in Formula I as set out herein. Compounds within the scope of Formula A may be prepared by a skilled person using the synthetic details in WO 95/00497 (Graham et al.) combined with the present specification. Preferred compounds for this aspect of the invention correspond to those set out in claims 6-12 of WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidin-2-yl-methyl moiety of the present invention replacing the $HS-CH_2-CH(NH_2)-CH-$ moiety on the left hand side of the relevant compounds attached to the piperazine ring as drawn out in the claims. A preferred compound is (2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine; see Example 7 herein.

Compounds of Formula I and III-V may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

When the compound contains a basic moiety it may form pharmaceutically acceptable salts with a variety of inorganic or organic acids, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. A suitable pharmaceutically-acceptable salt of the invention when the compound contains an acidic moiety is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically-acceptable cation, for example a salt with

methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Solvates, for example hydrates, are also within the ambit of the invention and may be prepared by generally known methods.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the Formula I. An in vivo hydrolysable ester of a compound of the formula (I) containing carboxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

According to another aspect of the invention there is provided a pharmaceutical composition comprising a compound as defined in any one Formulas I, III, IV or V or an individual compound listed above together with a pharmaceutically acceptable diluent or carrier. A preferred pharmaceutical composition is in the form of a tablet.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by

inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as

polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures

using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a steril injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board). Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may

vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of farnesylation of ras.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

Compounds of this invention may be useful in combination with known anti-cancer and cytotoxic agents. If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

According to another aspect of the invention there is provided a compound of Formula I, III, IV or V or a pharmaceutically-acceptable salt thereof, for use as a medicament.

According to another aspect of the invention there is provided a compound of Formula I, III, IV or V or a pharmaceutically-acceptable salt thereof, for use in preparation of a medicament for treatment of a disease mediated through farnesylation of ras.

According to another aspect of the present invention there is provided a method of treating ras mediated diseases, especially cancer, by administering an effective

amount of a compound of Formula I, III, IV or V or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Diseases or medical conditions may be mediated alone or in part by farnesylated ras. A particular disease of interest is cancer. Specific cancers of interest include:

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin;
- hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukemia, B-cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;
- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

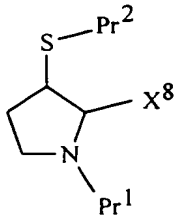
The compounds of Formula I, III, IV or V are especially useful in treatment of tumors having a high incidence of ras mutation, such as colon, lung, and pancreatic tumors. By the administration of a composition having one (or a combination) of the compounds of this invention, development of tumors in a mammalian host is reduced.

Compounds of Formula I, III, IV or V may also be useful in the treatment of diseases other than cancer that may be associated with signal transduction pathways operating through Ras, e.g., neuro-fibromatosis.

Compounds of Formula I, III, IV or V may also be useful in the treatment of diseases associated with CAAX-containing proteins other than Ras (e.g., nuclear lamins and transducin) that are also post-translationally modified by the enzyme farnesyl protein transferase.

Although the compounds of the Formula I, III, IV or V are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of activation of ras by farnesylation. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

According to another aspect of the invention there is provided a process for preparing compounds Formula I or of classes i), ii) or iii) as defined above which comprises deprotecting a compound of Formula VI



Formula VI

wherein X^8 represents the right hand side of compound classes i), ii) or iii) as defined above or X^8 represents the right hand side of Formula I, Pr^1 is H or an amino protecting group, Pr^2 is H or a thio protecting group and any functional groups in X^8 are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically acceptable salt thereof.

Compounds outside the scope of Formulas I or III-V having a 4-sulfanyl pyrrolidine moiety (compared with the 3-sulfanyl pyrrolidine moiety of the present invention) are known as intermediates in carbapenem side chain synthesis. The reader is referred to the following publications in this regard in respect of background synthetic details for assistance in compound preparation: Matsumura, Heterocycles (1995), 41, 147-59; European patent application EP 590885 (Zeneca; Betts *et al*); European patent application EP 592167 (Zeneca; Siret); European patent application EP 562855 (Zeneca; Jung *et al*); International patent application WO 92/17480 (Imperial Chemical Industries; Betts *et al*); European patent application EP 508682 (Imperial Chemical Industries; Betts *et al*); European Patent Application EP 280771 (Fujisawa Pharmaceutical, Murata *et al*); and International patent application WO 92/17479 (Imperial Chemical Industries; Betts *et al*).

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Such processes are illustrated by the following representative schemes in which variable groups have any of the meanings defined for Formula I unless stated otherwise. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting groups (as well as means of formation and eventual deprotection), see T.W.

Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991. Note abbreviations used have been listed immediately before the Examples below.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl; lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis.

Examples of hydroxy protecting groups include lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl,

t-butyldimethylsilyl, t-butyldiphenylsilyl); aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl).

Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g.. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

Compounds of Formula I in which L represents $-CO-NR^{16}-$ may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1.

Compounds of Formula I in which L represents -CO-NR^{25}-T- may be prepared by an analogous procedure. Suitable coupling conditions include the following.

i) Use of EEDQ at room temperature in an organic solvent (e.g. dichloromethane, methanol).

ii) Use of oxalyl chloride in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at 0° to room temperature for 0.5-16h.

iii) Use of EDC/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).

iv) Use of DCCI/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).

v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).

vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).

vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Compounds of Formula I in which L represents -CH_2NR^{18}-, -CH_2O- or -CH_2S- may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{18}. Suitable coupling conditions include the following.

i) Use of an inorganic base (e.g. $NaHCO_3$, NaH, K_2CO_3, butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about 70° to 150°

ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature -150°

iii) Use of an inorganic base (e.g. KOH, NaOH, K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Compounds of Formula I in which L represents -CH=CR^{20}- may be prepared using a Wittig reaction as outlined in Scheme 3. Suitable reaction conditions include the following.

i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in non-polar solvents such as 1,4,7,10,13-pentaoxacyclopentadecane (also called 15-Crown-5) or 1,4,7,10,13,16-hexaoxacyclooctadecane (also called 18-Crown-6).

Compounds of Formula I in which L represents -CH_2-NR^{18}- may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

i) Use of a reducing agent (e.g. $NaCNBH_3$, BH_3, hydrogen plus catalyst, $LiHBEt_3$, di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol & acetic acid.

Aldehyde (2) may be prepared by oxidation of the corresponding alcohol (1) under suitable conditions such as use of an oxidising agent (e.g. TPAP, NMM-O) in the presence of an organic solvent (e.g. acetonitrile, dichloromethane) at room temperature. Other suitable oxidising agents include chromium oxide, pyridinium chlorochromate, pyridinium dichromate, sodium dichromate and sodium hypochlorite.

Aldehyde (2) may also be prepared by reduction of the corresponding ester (1) under standard conditions using for example diisobutyl-aluminium hydride.

Compounds of Formula I in which L represents -CH_2-NR^{21}-T-, -CH_2-O-T- or -CH_2-S-T- may be prepared as outlined in Scheme 5 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or NR^{21}. Suitable coupling conditions are as outlined above in relation to Scheme 2. Optionally the positions of LG and XH in compounds 1 & 2 in Scheme 5 can be reversed to give the same end product.

Compounds of Formula I in which L represents -CH_2-NR^{23}-SO_2- may be prepared as outlined in Scheme 6. Compounds 1 & 2 may be coupled under standard conditions such as the following.

i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane) at a temperature range of 0°- 40°

ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of 0°-150°

Compounds of Formula I in which L represents -CH_2-NR^{24}-CO-T- may be prepared as outlined in Scheme 7. Compounds 1 & 2 may be coupled under standard conditions such as described above for L = -CO-NR^{16}- .

Compounds of Formula I in which L represents -CH_2-CHR^{19}- may be prepared as by reduction of compounds of the type set out as compound 3 in Scheme 3 but substituting R^{19} in lieu of R^{20}. Reduction is carried out under standard conditions with standard reagents for example using hydrogenation in the presence of a catalyst such as palladium on charcoal at room temperature.

Biological activity was tested as follows. Farnesyl protein transferase (FPT) was partially purified from human placenta by ammonium sulphate fractionation followed by a single Q-Sepharose® (Pharmacia, Inc) anion exchange chromatography essentially as described by Ray and Lopez-Belmonte (Ray K P and Lopez-Belmonte J (1992) Biochemical Society Transations 20 494-497). The substrate for FPT was Kras (CVIM C-terminal sequence). The cDNA for oncogenic val12 variant of human c-Ki-ras-2 4B was obtained from the plasmid pSW11-1 (ATCC). This was then subcloned into the polylinker of a suitable expression vector e.g. pIC147. The Kras was obtained after expression in the E. coli strain. BL21. The expression and purification of c-KI-ras-2 4B and the val12 variant in E. coli has also been reported by Lowe et al (Lowe P N et al. J. Biol. Chem. (1991) 266 1672-1678).

Incubations with enzyme contained 300nM tritiated farnesyl pyrophosphate (DuPont/New England Nuclear), 120nM ras-CVIM, 50mM Tris HCl pH 8.0, 5mM $MgCl_2$, 10μM $ZnCl_2$, 5mM dithiothreitol and compounds were added at appropriate concentrations in DMSO (3% final concentration in test and vehicle control). Incubations were for 20 minutes at 37 ° and were stopped with acid ethanol as described by Pompliano et al. (Pompliano D L et al (1992) 31 3800-3807). Precipitated protein was then collected onto glass fibre filter mats (B) using a Tomtec® cell harvester and tritiated label was measured in a Wallac®1204 Betaplate scintillation counter.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general compounds of the Formula I possess an IC_{50} in the above test in the range, for example, 0.001 to 200μM. Thus by way of example the compound of Example 2 herein has an IC_{50} of approximately 0.42μM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t or tr, triplet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

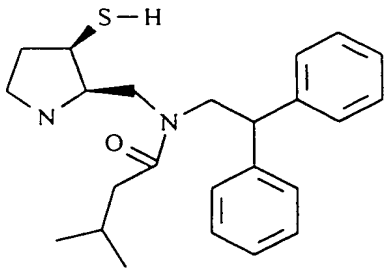
(viii) the following abbreviations have been used:-

BOC	tert-butoxycarbonyl
DCCI	1,3-dicyclohexylcarbodiimide
DMA	N,N-dimethylacetamide
DMAP	4-dimethyl-aminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
HOBT	1-hydroxybenzotriazole
NMM	N-methylmorpholine
NMM-O	4-methylmorpholine-N-oxide
RT	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSI	trimethylsilyliodide
TPAP	tetrapropylammonium perruthenate

Note in the Schemes only those hydrogen atoms thought to assist clarity have been illustrated (ie not all hydrogen atoms have been illustrated).

Example 1

3-methyl-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-butyramide (compound 14a)



1. A solution of starting material 3-methyl-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-1-BOC-3-tritylsulfanyl-pyrrolidin-2-ylmethyl)- butyramide (compound 12a; 0.265g), triethyl silane(0.25 ml) in dichloromethane(2 ml) was treated with trifluoroacetic acid(16 ml) and

the mixture stirred under an argon atmosphere for 30 minutes at ambient temperature and then evaporated under reduced pressure to remove most of the solvents. The residue was taken up in ethyl acetate(2 ml) and treated with 1.0M ethereal HCl. The ethyl acetate was evaporated away and diethyl ether(5 ml) and iso-hexane(20ml) were added . The gummy solid obtained gradually solidified and was isolated by centifugation, washed with more ether(5 ml)/iso-hexane(20 ml) and dried under high-vacuum to give the desired end product as a white solid(0.125g).

NMR data ($CDCl_3$) ; δ0.80-0.95(m,6H), 1.85-2.50(m,6H), 3.00-3.15(m,1H), 3.30-3.60(m,3H), 3.75-4.30(m,4H), 7.20-7.40(m,10H), 7.60(br.s,1H), 8.67(br.s,1H), 11.20(br.s,1H)

Micro Analysis	%Theory C65.2, H7.89, N6.19.
(1.0 HCl,0.5H_2O,0.14Et_2O)	%Found C65.2, H8.00, N6.0

2. The starting material was prepared as follows. 3-Tritylsulfanyl-pyrrolidine-2-carboxylic acid (compound (4)) was prepared from methyl 3-bromo-3,4-dihydro-2H-pyrrole-2-carboxylate (compound (1)) by the route described in Liebigs Ann. Chem. 1981, 1073-1088. In brief, the methyl ester of the 2-carboxylate group of compound 1 was converted to the sodium salt of the carboxylic acid using aqueous NaOH at 0-5°; the 3-bromo dihydropyrrole was then converted to 3-tritylsulfanylpyrrolidine using triphenylmethylmercaptan in the presence of DME and aqueous NaOH at 0-5°; then compound (4) was formed by using sodium borohydride then 1M HCl.

Di-tert.-butyl dicarbonate(0.24g) was added to a stirred mixture of compound (4) (0.39g) and triethylamine(0.31 ml) in dichloromethane(3 ml) cooled to 0° C under an argon atmosphere. The mixture was allowed to warm up to ambient temperature and stirred for 60 h. It was then washed with 2M. aqueous sodium hydroxide,1.0M. citric acid and finally brine and then dried . The solvent was evaporated under reduced pressure to give 1-BOC-3-tritylsulfanyl-pyrrolidine-2-carboxylic acid (5) as a solid foam (0.446g).

3. A mixture of 1-hydroxybenztriazole(0.142g), EDC(0.192g), 4-methylmorpholine(0.24ml) and compound(5)(0.446g) in dichloromethane(10 ml) was stirred at 5° C for 20minutes and then for 16 h. at ambient temperature. The mixture was then washed with 1.0M citric acid and brine, dried and the solvent evaporated under reduced pressure. The product was purified by column chromatography eluting with ethyl

acetate/iso-hexane(15:85) to give 1-(1-BOC-3-tritylsulfanyl-pyrrolidin-2-carbonyl)-benzotriazole (compound(6)) as a solid foam(0.193g).

NMR data ($CDCl_3$) ; δ1.45+1.49(s,s,9H), 2.17-2.40(m,2H), 3.08-3.27(m,2H), 3.50-3.72(m,2H), 7.21-7.61(m,18H), 8.02(dd,1H)

4. A mixture of compound(6)(0.087g), N,O-dimethylhydroxylamine HCl (0.028g) and 4-dimethylaminopyridine(0.039g) in dichloromethane(2 ml) was stirred at ambient temperature for 16 h. More N,O-dimethylhydroxylamine(0.056g) and DMAP(0.078g) were added and the stirring was continued for another 16 h. The reaction was filtered and the filtrate applied directly to a chromatography column which was eluted with ethyl acetate/iso-hexane(15:85) to give (2R,3R)- 1-BOC-3-tritylsulfanyl-N-methoxy-N-methylpyrrolidine-2-carboxamide (compound(8)) as a white solid(0.06g). (Note the 2S,3R stereoisomer was also formed).

NMR data ($CDCl_3$) ; δ0.90–1.05(m,1H), 1.37+1.39(s,s,9H), 1.95-2.15(m,1H), 2.80-3.05(m,2H), 3.27+3.30(s,s,3H), 3.35-3.53(m,1H), 3.83+3.98(s,s,3H), 4.80-5.15(m,1H), 7.15-7.50(m,15H).

5. A solution of lithium aluminium hydride (7.0ml) in diethyl ether(1.0M) was added dropwise over 10 minutes to a stirred solution of compound(8)(3.35 g) in THF(35 ml) cooled to -10° C under an argon atmosphere. After the addition was complete the reaction was allowed to warm to +5° C for 10 minutes and then cooled to -35° C. A solution of potassium bisulphate(1.72g in 6 ml water) was carefully added and the mixture was then allowed to warm to ambient temperature and stirred for a further 1h. It was then filtered through diatomaceous earth (Celite®) and the filtrate diluted with diethyl ether(50 ml). The organic solution was washed with 10% citric acid, saturated sodium bicarbonate, brine, dried and the solvent removed under reduced pressure to give (2R,3R)-1-BOC-3-tritylsulfanyl-pyrrolidine-2-carbaldehyde (compound(9)) as a solid foam(3.04g).

NMR data ($CDCl_3$) ; δ1.32+1.37(s,s,9H), 1.65-2.05(m,2H), 3.00-3.70(m,4H), 7.20-7.53(m,15H), 9.42+9.54(s,s,1H)

6. Compound(9)(0.5 g) in dichloromethane(5 ml) was added to a stirred mixture of 2,2-diphenylethylamine(0.25 g), powdered 4 A molecular sieve(1.0 g) and sodium triacetoxy borohydride(0.27 g) in dichloromethane(20 ml) cooled to -20 ° C under an argon atmosphere. The reaction mixture was then allowed to warm to ambient temperature and stirred for another 18h. The mixture was filtered through diatomaceous earth and the

filtrate washed with saturated aqueous sodium bicarbonate solution and brine. The organic solution was dried and then the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with 1.ethyl acetate/iso-hexane(20:80), 2.(30:70) to give (2R,3R)-1-BOC-N-(2,2-diphenylethyl)-3-tritylsulfanyl-pyrrolidin-2-yl-methylamine (compound(10)) as a foam(0.547 g).

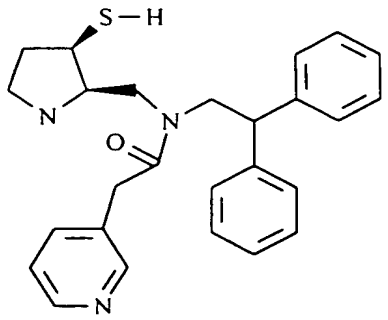
NMR data ($CDCl_3$) ; δ1.32+1.35(s,s,9H), 1.70-1.95(m,2H), 2.50-3.55(m,8H), 4.05-4.18(m,1H), 7.10-7.48(m,25H)

7. A mixture of iso-valeryl chloride(0.05 ml), compound(10)(0.25 g) and triethylamine(0.11 ml) in dichloromethane(10 ml) was stirred at ambient temperature under an argon atmosphere for 3h. The reaction was applied directly to a silica chromatography column which was eluted with 1.ethyl acetate/iso-hexane(15:85),2.(17:83),3.(20:80) to give the desired starting material (compound(12a)) as a white solid(0.292 g).

NMR data ($CDCl_3$) ; δ0.60+0.70+0.82(d,dd,d,6H), 1.05-1.25(m,1H), 1.30+1.33+1.36(s,s,s,9H), 1.55-4.95(m,13H), 7.05-7.50(m,25H)

Example 2

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-acetamide (compound 14b)



Compound(14b) was prepared by an analogous procedure with that described for preparation of compound(14a) in Example 1.

NMR data ($CDCl_3$) ; δ2.10–2.25(m,1H), 2.35-2.55(m,1H), 3.15-3.53(m,4H), 3.55-3.95(m,3H), 4.00-4.25(m,1H), 4.30-4.55(m,3H), 7.10-7.50(m,12H), 7.55-7.75(m,1H), 8.07-8.20(m,1H), 8.38-8.55(m,1H), 8.70(s,1H), 9.38-9.60(m,1H), 10.25-10.43(br.s,1H).

Micro Analysis: %Theory C58.8, H6.45, N7.91.

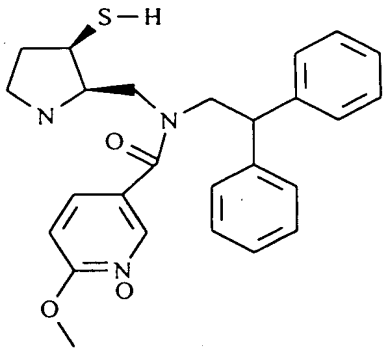
(2.0 HCl,1.5H_2O) %Found C58.6, H6.10, N7.70

Starting material 2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)-acetamide (compound(12b)) was prepared as follows. A mixture of HOBT(0.076g), EDC(0.103g), 4-methylmorpholine(0.23 ml) and compound(10)(see Example 1; 0.269 g) and 3-pyridylacetic acid(0.093g) in dichloromethane(12 ml) was stirred at 5° C for 15 minutes and then at ambient temperature for 20h. The solution was then applied to a silica chromatography column which was eluted with 1.ethyl acetate/iso-hexane(30:70), 2.(60:40), 3.(90:10) and 4.ethyl acetate to give the desired starting material as a white solid (0.217 g).

NMR data ($CDCl_3$) ; δ1.05-1.25(m,1H), 1.37(s,9H), 1.70-4.50(m,12H), 7.05-7.55(m,27H), 7.78-8.50(m,2H)

Example 3

6-Methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)- pyridine-3-carboxamide (compound 14c)



Compound(14c) was prepared by an analogous procedure with that described for preparation of compound(14a) in Example 1.

NMR data ($CDCl_3$) ; δ1.15-1.35(m,1H), 1.88-2.03(m,1H). 2.21(d,1H), 2.28-2.50(m,1H), 3.00-3.20(m,1H). 3.20-3.37(m,1H), 3.42-3.55(m,1H), 3.69(d,1H), 3.80-3.98(m,1H), 4.05(s,3H), 4.20-4.40(m,3H). 6.58(d,1H), 7.08-7.36(m,11H), 8.11(s,1H), 9.10(br.s,1H), 10.8(br.s,1H)

Micro Analysis: %Theory C60.0, H6.59, N8.08.

(1.0 HCl,1.0H_2O) %Found C59.6, H6.00, N7.80

Starting material 6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)- pyridine-3-carboxamide (compound 12(c)) was prepared from compound (10) (see Example 1) using the method described for compound (12b- Example 2) using appropiate intermediates.

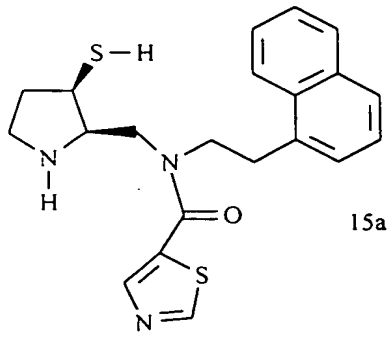
NMR data ($CDCl_3$) ; δ0.75-1.00(m,1H), 1.10-1.25(m,1H), 1.25-1.45(m,9H), 1.90-3.75(m,8H), 3.90-4.15(m,3H), 4.20-4.90(m,1H), 6.30-6.55(m,1H), 6.60-7.50(m,27H)

Example 4

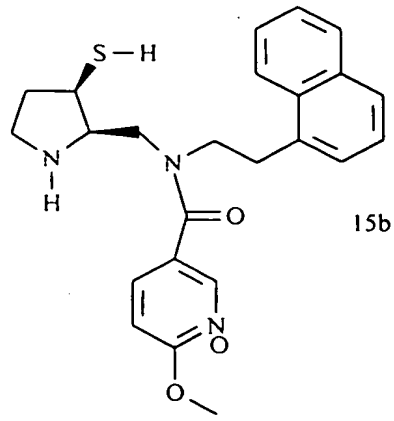
Preparation of

a) **N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide** (compound 15a); and

b) **6-Methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)- pyridine-3-carboxamide** (compound 15b)



15a



15b

Compound(15a) and compound(15b) were prepared by analogous procedures to those described for preparation of compound(14a) in example 1. The starting materials for compounds (15a) and (15b) were prepared from compound (9) (Example 1) using appropiate intermediates by the procedures described in the synthesis of compounds (12a) and(12b). In brief, the following reagents were used with respect to the steps numbered in Example 1.

Step 6: 1-naphthylamine/ Na triacetoxyborohydride/ molecular sieve/ -20°

Step 7: thiazole-5-carboxylic acid (for 15a) or 6-methoxynicotinic acid N-oxide (for 15b)/ EDC/ HOBT/ 4-methylmorpholine.

Characterisation data is set out below.

Compound(15a):

NMR data (DMSO-d6) ; δ1.90-2.05(m,1H), 3.10-4.10(m,9H), 7.30-7.95(m,8H), 8.12(s,1H), 9.08(s,1H), 9.30(br.s,1H), 10.05(br.s,1H)

Micro Analysis: %Theory C52.6, H5.47, N8.76

(2.0 HCl,0.5H_2O) %Found C52.7, H5.3, N8.5

Compound(15b):

NMR data ($CDCl_3$) ; δ2.30-2.45(m,2H), 1.90-4.15(m,14H), 6.27(d,1H), 6.90-8.05(m,10H). 9.20(br.s,1H), 10.60(br.s,1H)

Micro Analysis: %Theory C57.7, H6.36, N8.24

(1.0HCl,1.5H_2O,0.12Et_2O) %Found C57.8, H6.0, N8.2

(2R,3R)-1-BOC-N-(naphthyl-1-ylethyl)-3-tritylsulfanyl-pyrrolidin-2-yl-methylamine which is the product (compound (11)) of the reaction equivalent to step 6 (Example 1):

NMR data ($CDCl_3$) ; δ 0.80-0.95(m, 1H), 1.34(s, 9H), 1.70-2.00(m, 1H), 2.50-3.65(m, 10H), 7.15-7.50(m, 19H), 7.65-7.73(m, 1H), 7.80-7.88(m, 1H), 8.00-8.12(m, 1H).

N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-1-BOC-3-tritylsulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide which is the product (compound (13a)) of the reaction equivalent to step 7 (Example 1) for synthesis of compound 15a.

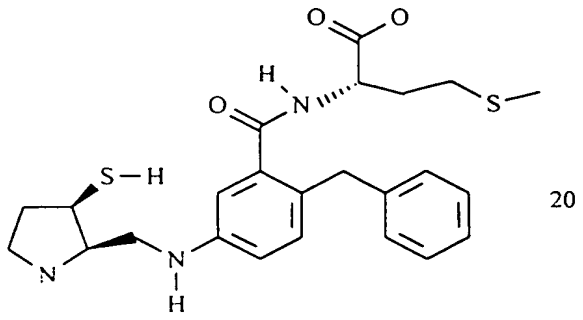
NMR data for 13a ($CDCl_3$) ; δ 0.80-0.95(m, 1H), 1.28(s, 9H), 1.80-4.40(m, 11H), 7.10-8.80(m, 24H).

6-Methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-1-BOC-3-tritylsulfanylpyrrolidin-2-ylmethyl)- pyridine-3-carboxamide which is the product (compound (13b)) of the reaction equivalent to step 7 (Example 1) for 15b:

NMR data for 13b ($CDCl_3$) ; δ 0.80-0.95(m, 1H), 1.30(s, 9H), 1.90-4.20(m, 14H), 5.95-6.10(m, 1H), 6.70-7.85(m, 24H).

Example 5

(2S)-2-{2-Benzyl-5-[([2R,3R]3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid



Isopropyl (2S)-2-{2-Benzyl-5-[([2R,3R]3-tritylsulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid (compound 18) was prepared by reacting compound 9 (Example 1) with isopropyl (2S)-2-(5-amino-2-benzyl-benzoylamino)-4-methylsulfanyl-butyric acid (compound 17) according to standard procedures. In brief, a solution containing compounds 9 and 17 in isopropyl alcohol was treated with powdered 4A° molecular sieves and the resulting suspension was stirred at room temperature for 1h. Acetic acid and sodium cyanoborohydride were then added and the reaction mixture was left to stir for 18h at room temperature. The reaction mixture was then partitioned between EtOAc(50mL) and saturated $NaHCO_3$(aq)(50mL). The aqueous phase was then washed with EtOAc(50mL) and the combined organics dried over $MgSO_4$, filtered and concentrated to a colourless gum. This was then purified by flash chromatography on SiO_2 (Varian Mega Bond Elut Column) eluting a gradient of 25-40% EtOAc/i-hexane to give compound 18.

Isopropyl (2S)-2-{2-Benzyl-5-[([2R,3R]3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid (compound 19) was prepared from compound 18 according to the method in Example 1, step1.

Compound 20 was prepared from compound 19 by standard procedures. In brief, 2N NaOH was added to a stirred solution of compound 19 in MeOH at room temperature under argon. After 18 h the reaction mixture was concentrated to remove the MeOH. The resulting residues were dissolved in H_2O(2.0 mL) and acidified to pH3 with 2N HCl. The resulting solution was purified by reverse phase HPLC (Dynamax C18,8μ prepcolumn), eluting with a gradient of 0-40% MeOH/H_2O. Product fractions were concentrated and the desired end product purified by standard methods.

H^1NMR (DMSO-D6 +CD_3COOD) 1.96(5H,m), 2.5(5H,m+DMSO),3.18-3.48(3.5H,m), 3.75-4.04 (3.5H,m), 4.46(1H,q), 6.61(2H,m,Ar), 6.94-7.23(6H,m,Ar).

MS (ESP+) m/z $(M+H)^+$ 474.

Anal. Calcd for $C_{24}H_{31}N_3S_2O_3$.1.6TFA C, 49.8; H, 5.01; N, 6.4; Found C, 49.5; H, 5.1; N, 6.4

Compound 17 was prepared as follows. A solution of methyl (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyric acid (compound 34d) (25.24g,62.78mmol) in MeOH (500mL) was treated with 2N NaOH (35mL,70mmol). The resulting solution was then evaporated to dryness and the solids partitioned between Et_2O (200mL) and water (500mL). The aqueous material was then acidified to pH2 with 2N HCl and extracted with EtOAc(2x250mL). The combined organics were washed with water(2x100mL), brine(100mL), filtered through phase separating paper and evaporated to give (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyric acid (compound 36a) as a white solid,23.57g(96.8%).

^{1}H NMR (DMSO-D_6,300MH_Z) d1.8-2.2(5H,m);2.3-2.6(2H+DMSO,m); 4.1-4.3(2H,m);4.4-4.6(1H,m);7.1-7.3(5H,m);7.4-7.6(1H,m);8.1-8.3(2H,m); 8.9-9.0(1H,m,NHCO)

MS (ESP-) m/z 387(M-H)$^-$.

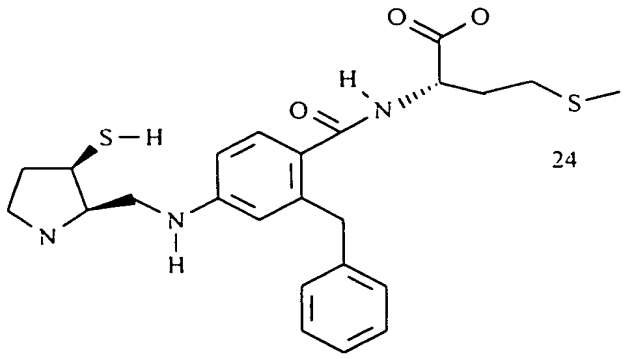
Sulphuryl chloride (5.0mL,62mmol) was added to a stirred suspension of compound 36a (19.2g,50mmol) in IPA (500mL). The resulting mixture was then heated at reflux for 18hrs. The reaction mixture was then evaporated to 1/5 volume and partitioned between EtOAc (1L) and saturated $NaHCO_3$(aq) (500mL).The organics were then washed with water (200mL), brine (200mL), filtered through phase separating paper and evaporated to give isopropyl (2S)-2-(2-benzyl-5-nitro-benzoylamino)-4-methylsulfanyl-butyric acid (compound 36b) as a white solid,21.25g(100%).

^{1}H NMR (DMSO-D_6,300MH_Z) d1.0-1.3(6H,m);1.8-2.2(5H,m);
2.3-2.6(2H+DMSO,m);4.1-4.3(2H,m);4.4-4.6(1H,m);4.8-5.0(1H,m);7.1-7.3(5H,m);
7.4-7.6(1H,m);8.1-8.3(2H,m);9.0(1H,m,NHCO)
MS (ESP+) m/z 431(M+H)+.

$SnCl_2.2H_2O$ (2.5g,11.08mmol) was added to a stirred solution of compound 36b (2.24mmol) in EtOAc(50mL) and the resulting mixture heated at reflux for 18hrs. The reaction mixture was cooled to RT and treated with 0.88S0 SG NH_3(aq) dropwise to pH8. The resulting precipitate was removed by filtration through diatomaceous earth. The filtrates were then evaporated and purified by chromatography (Mega Bond Elut,SiO2), eluting with CH_2Cl_2 and then 50%EtOAc/ i-hexane to give the desired aniline compound (17).

Example 6

(2S)-2-{2-Benzyl-4-[([2R,3R]3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid



24

Compound 24 was prepared from compound (9) (Example 1) and methyl (2S)-2-(4-amino-2-benzyl-benzoylamino)-4-methylsulfanyl-butyric acid (compound 21) according to procedures outlined in Example 5.
H^{1}NMR (DMSO-D6 +CD_3COOD) 1.98(5H,m), 2.48(5H,m),3.18-3.46(3.5H,m), 3.75(1H,m), 3.9-4.2(2.5H.m), 4.43(1H,m), 6.46(2H,m,Ar), 7.04-7.34(6H,m,Ar).
MS (ESP+) m/z (M+H)+ 474.
Microanalysis, calculated for C24H31N3S2O3.1.55TFA: C, 50.0; H, 5.04; N, 6.46; Found C, 49.9; H, 5.1; N, 6.4.

Compound(21) used in the preparation of compound (24) was prepared as follows. Sodium dichromate dihydrate (151gm) was added to (575ml) glacial acetic acid followe by 2-bromo-4-nitro-toluene (25) (49.7gm). To this solution was added dropwise sulphuric acid (175ml) at such a rate to maintain the temperature between 75-85°C. This mixture was heated to 100-110°C for 3h cooled to 50°C and poured onto ice (1litre). The aqueous phase was extracted with ethyl acetate, the organic layer back extracted with NaOH and the resulting basic aqueous layer acidified with HCl . The precipitated solid was filtered, washed with water and air dried to give 15.72 gm (28%) of 2-bromo-4-nitro-benzoic acid (compound (26)) as a white solid.

NMR H^1NMR $CDCl_3$ 7.42 (1H,d),8.08 (1H,q),8.42 (1H,d)

Compound (26) in MeOH was treated with SO_2Cl_2 and the resulting solution heated at reflux for18h. The reaction mixture was then evaporated ,pre-absorbed on SiO_2 (Merck,9385) and chromatographed, eluting with 10%EtOAc/i-Hexane. Appropriate fractions were combined and evaporated to give methyl 2-bromo-4-nitro-benzoic acid (compound (27)).

A solution of benzyl bromide (2.0mL,17.3mmol) in THF(10mL) was added dropwise at 0°C to a stirred suspension of zinc dust(1.7g,26mmol) in THF(10mL) which had been activated according to the method described by Knochel (J.O.C. 53, 2392, 1988). The mixture was left to warm to RT and stir for 3hrs. An aliquot (6.5mmol) of the supernatent containing the benzyl zinc reagent was then added to a stirred solution of compound 27 (3.85mmol) and $Pd(dba)_2$ (0.0385mmol) in THF(10mL) at RT under argon. After 1hr a second aliquot (6.5mmol) of the benzyl zinc reagent was added. The resulting black reaction mixture was quenched with 2N HCl (250mL) and extracted with EtOAc (2x100mL). The combined organics were washed with water (50mL) and brine (50mL),filtered through phase separating paper and evaporated to an orange gum. This was chromatographed on SiO_2 (Merck,9385) eluting with 10%EtOAc/i-hexane to give methyl 2-benzyl-4-nitro-benzoic acid (compound (28)).

2N NaOH (2.0mL,4mmol) was added to a solution of compound (28) (2.06mmol) in MeOH (10mL) at RT. After 2hrs the reaction mixture was evaporated to remove the MeOH and then partitioned between Et_2O (20mL) and 2N NaOH (20mL). The aqueous phase was acidified to pH2/3 with 2N HCl and extracted with EtOAc(3x20mL). The combined organics were washed with water (20mL) and brine (20mL), filtered through

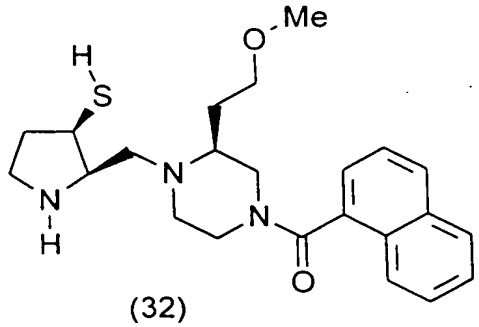
phase separating paper and evaporated to yield 2-benzyl-4-nitro-benzoic acid (compound (29)).

Compound (29) (2.45mmol) was coupled with L-methionine methyl ester hydrochloride (540mg,2.7mmol) to give methyl 2-[(2-benzyl-4-nitro-benzoyl)amino]- 4-methylsulfanyl-butyric acid (30).

$SnCl_2 2H_2O$ (2.5g,11.08mmol) was added to a stirred solution of compound (30) (2.24mmol) in EtOAc(50mL) and the resulting mixture heated at reflux for 18h. The reaction mixture was cooled to RT and treated with 0.88S0 SG NH_3(aq) dropwise to pH8. The resulting precipitate was removed by filtration through diatomaceous earth (Celite®)(545). The filtrates were then evaporated and purified by chromatography (Mega Bond Elut,SiO_2),eluting with CH_2Cl_2 and then 50%EtOAc/ i-hexane to give the desired compound (21).

Example 7

(2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine



(32)

Compound (32) was synthesised from starting material (2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-1-BOC-3-tritylsulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine (compound (31)) analogously with the procedure in Example 1, step 1.

NMR data ($CDCl_3$) ; δ 1.70–4.90(m, 24H), 7.35-8.00(m, 7H), 9.40-10.30(br.s, 1H), 10.50-11.80(br.s, 1H).

Micro Analysis: %Theory C54.0, H7.20, N8.01

(2.0HCl,1.5H_2O,0.15Et_2O) %Found C54.3, H7.00, N8.00

The starting material was prepared as follows. Compound (31) was synthesised from compound (8) (see Example 1) and (3S)-3-(2-methoxy-ethyl) -1-naphthoyl-piperazine

(compound (16)) by the method described in Example 1, step 6, for the preparation of compound (10). Compound (16) was prepared using analogous methods to those descri in International Patent Application WO 95/00497 (Merck; Graham et al); see compound VIII, Scheme 2 and Example 7, Step E therein substituting naphthoic acid in lieu of 2,3-dimethylbenzoic acid.

NMR data, compound (31), ($CDCl_3$) ; δ 0.80-1.20(m, 1H), 1.30-1.43(m, 9H), 1.75-3.75(m, 20H), 3.95-4.55(m, 1H), 7.15-7.95(m, 22H).

Example 8

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	488.5
	Magnesium	1.5

(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	1M Sodium hydroxide solution	15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)	
	Polyethylene glycol 400	4.5% w/v
	Water for injection to 100%	

(f)	Injection II	(10 mg/ml)
	Compound X	1.0% w/v
	Sodium phosphate BP	3.6% w/v
	0.1M Sodium hydroxide solution	15.0% v/v
	Water for injection to 100%	

(g) Injection III (1mg/ml, buffered to pH6)

Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

(h) Aerosol I

	mg/ml
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i) Aerosol II

	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j) Aerosol III

	mg/ml
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k)	Aerosol IV	mg/ml
	Compound X	2.5
	Soya lecithin	2.7
	Trichlorofluoromethane	67.5
	Dichlorodifluoromethane	1086.0
	Dichlorotetrafluoroethane	191.6

(l)	Ointment	ml
	Compound X	40 mg
	Ethanol	300 µl
	Water	300 µl
	1-Dodecylazacycloheptan-2-one	50 µl
	Propylene glycol	to 1 ml

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

PCT/GB 94/02212

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General Pharmaceutical